Learning and Memory Enhancement by Neuropeptides
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The major purpose of this work was to study biochemical mechanisms responsible for the toxic effects of the organometal neurotoxin trimethyltin on learning, in order to develop strategies for prevention or alleviation of toxicity. Trialkyltins are used as stabilizers for plastics, or as biocide for control of fungus, barnacles, bacteria and insects. These compounds are anti-fouling toxicants of specific interest to the Navy, because of potential of estuarine contamination from naval vessels, and as a danger to seamen on ships carrying paint containing these compounds, since desalinated water used on these vessels may become contaminated. These compounds are also of interest as a model treatments for study of learning/memory dysfunction resulting from exposure to other toxicants (e.g. other heavy metals, organic solvents), or arising from disease states. We study learning in an autoshaping task, in which rats learn to touch a lever to obtain food. Substantial progress towards the goals of the project were made, especially considering the limited budget. The following papers were published with ONR support:

M.S. Huang, R.B. Messing and S.B. Sparber, Learning enhancement and behavioral arousal induced by an anxiogenic drug, Life Sciences 41(1987): 1083-1088.

C.A. Cohen, R.B. Messing and S.B. Sparber, Selective learning impairment of delayed reinforcement autoshaped behavior caused by low doses of trimethyltin, Psychopharmacology 93(1987): 301-307.

S.B. Sparber, C.A. Cohen and R.B. Messing, Reversal of a trimethyltin-induced learning deficit by desglycinamide-8-arginine vasopressin, Life Sciences 42(1988): 171-177.

E.N. Gerbec, R.B. Messing and S.B. Sparber, Parallel changes in operant behavioral adaptation and hippocampal corticosterone binding in rats treated with trimethyltin. Brain Research 460(1988) 346-351.

R.B. Messing, G. Bollweg, Q. Chen and S.B. Sparber, Dose-specific effects of trimethyltin poisoning on learning and hippocampal corticosterone binding. Neurotoxicology 9(1988) 491-502.

R.B. Messing, S.J. Allen, L. Aanonsen and S.B. Sparber, Naloxone administration impairs autoshaped learning. Behavioral and Neural Biology 51 (1989)34-45.

The following papers have been submitted for publication:

S.B. Sparber, G. Bollweg and R.B. Messing, Food deprivation enhances autoshaped and latent inhibiton of autoshaped behavior: interpretation and theoretical considerations.

V. Devauges, R.B. Messing and S.J. Sara, Clonidine-induced sedation is reduced by the limbic forebrain neurotoxin trimethyltin.

In addition, the following abstracts were presented at scientific meetings:

S.B. Sparber, G. Seran, R.B. Messing, J. O'Callaghan and B. Berra, Toxicity of mixed gangliosides (GS): Learning and hippocampal corticosterone receptors, Xth International Congress of Pharmacology Abstracts, 1987.

R.B. Messing, S.Allen, L. Aanonsen and S.B. Sparber, Post-session naloxone administration impairs autoshaped lever response learning, Society for Neuroscience Abstracts 13(1987): 654.

S.B. Sparber, C.A. Cohen and R.B. Messing, Desglycinamide-8-arginine vasopressin reverses a trimethyltin-induced learning defici*, Society for Neuroscience Abstracts 13(1987): 654.

R.B. Messing, G. Bollweg, Q. Chen and S.B. Sparber, Dose-specific impairments in autoshaped behaviors and hippocampal corticosterone binding induced by trimethyltin (TMT). Presented at the Eighth European Winter Conference on Brain Research, Tignes, France, March, 1988.

Messing, R.B. and Aanonsen, L.A. Trimethyltin (TMT) effects on hippocampal phencyclidine receptors: Dose-dependent decreases in CA and increases in dentate. Society for Neuroscience Abstracts 15 (1989):1351.

Thus, in the three years and ninety days the ONR supported this project before termination, for a budget of $187,830, eight full length research publications and five abstracts were produced. These represent the following scientific accomplishments:

1. The demonstration that trimethyltin produces dose-related damage to the hippocampus and related olfactory cortex, but that the severity of the lesion at the different doses causes qualitatively different behavioral and biochemical sequelae. This is of enormous signficance, since

a) it indicates that dementing processes may produce remarkably qualtitatively different symptoms at different stages of the process, rather than a simple increase in the same symptoms.

b) it indicates that adaptive biochemical changes, particularly in less damaged organisms may be as responsible for functional impairment as the initial insult (brain lesion).

2. The finding that corticosterone receptors in hippocampus are reduced by a moderate dose of trimethyltin, providing for the first time a simple animal preparation with which to examine the functions of the hippocampal corticosterone system.

3. The finding that cognitive impairments induced by trimethyltin can be attenuated by the vasopressin analog desglycinamide arginine vasopressin or by gangliosides, but that gangliosides are themselves toxic. This finding is of particular significance because

a) gangliosides have been given prophylactically to humans with degenerative diseases, and this practice may have very adverse consequences

b) gangliosides by themselves produce a behavioral syndrome comparable to that seen with a moderate dose of trimethyltin, as well as a decrease in hippocampal corticosterone receptors, but without loss of cells in the hippocampus. This strengthens the interpretation that the decrease in hippocampal corticosterone binding seen with trimethyltin is a down-regulatory response and not just the consequence of loss of neurons.

4. The demonstration that naloxone administration impairs learning and memory of our autoshaping task. This stands in contrast to earlier work of the P.I. and others showing that naloxone generally enhances memory. This variability of naloxone's effects in different tasks may explain the disappointing clinical research with naloxone in memory-impaired humans.

5. The demonstration that yohimbine enhances learning of our autoshaping task, but that this may be due to an increase in behavioral arousal (which might be useful under certain circumstances, e.g. in the treatment of the cognitive impairment of depression). This demonstrates the power of our methodology in delineating the behavioral mechanisms of action of drugs.

6. The demonstration that trimethyltin produces a dose-dependent decrease in phencyclidine receptors in the hippocampal gyrus, but an increase in the dentate. The phencyclidine receptor is co-localized with the glutamate NMDA receptor, and NMDA neurotransmission has been implicated in learning and memory formation and in excitotoxic (e.g. seizure-induced) damage. Thus, this work, while just begun, is of great potential, since it indicates that part of the mechanism of action of trimethyltin (which is at present unknown) may be related to NMDA excitotoxicity. Further, the cognitive impairment seen with trimethyltin may be related to loss of these receptors which is moderate at a low dose, but severe at the high dose. However, the increase in the dentate gyrus at the high dose may also be an up-regulation which could be involved in part of the behavioral syndrome at this dose.

7. The demonstration that the sedative effect of clonidine is impaired in rats treated with trimethyltin. This effect was predicted from earlier research showing that there is an up-regulation of adrenergic receptors in rats given trimethyltin. Thus, this work is important, since it is the first work showing that we can indeed make predictions of drug and behavioral effects based upon our detailed knowledge of the effects of these brain

lesions. Also, this work may help to explain the anomalous effects of clonidine in aged or otherwise impaired subjects (e.g. people with Korsakoff's psychosis).

Projects 6. and 7. represent collaborations with colleagues in the Department of Neuroanatomy and Cell Biology at the University of Minnesota and with colleagues in France, at the C.N.R.S. These collaborations bore enormous promise before the untimely demise of this project.

Rita B. Messing

Rita B. Messing, Ph.D., P.I.
Associate Professor of Pharmacology
and Neuroscience
Department of Pharmacology
University of Minnesota Medical School
3-260 Millard Hall
435 Delaware St. S.E.
Minneapolis, MN 55455
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